Nephrology Grand Rounds
Mansi Mehta
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Clinical Case

CC: 75yo M from Ecuador presenting with progressive LE edema and AKI

HPI: Patient was recently diagnosed w/ Smoldering Myeloma after a hospitalization for syncope revealed uncontrolled HTN, proteinuria and labs concerning for MM - He was being followed in hematology clinic and then presented to the ED 2 months after diagnosis with abdominal distension and new LE edema
- PMH: BPH and Hyperlipidemia
- PSH: none
- SH: no history Tobacco/EtOH/Illlicit drug abuse; visiting from Ecuador
- FH: father with heart disease; no h/o of malignancy or renal disease
- Meds: tamsulosin and pravastatin
- Allergies: KNDA

- ROS: +LE edema, DOE, increased abdominal distention, decreased appetite
Physical Exam

- VS: Afebrile, BP: 115/75 P: 16 R: 64 O2sat: 96% on 2L NC
- Gen: NAD, elderly Hispanic M, chronically-ill appearing
- HEENT: no lymphadenopathy
- CVS: +s1s2, RRR, +systolic murmur along R sternal border. No JVD
- Resp: decreased BS at bases
- Abdomen: moderately distended, NT, +ascites
- Extremities: pitting edema of B/L LE up to mid-thighs
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<th>Value</th>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>8.4</td>
<td>Sodium</td>
<td>142</td>
<td>Total Protein</td>
<td>5.8</td>
</tr>
<tr>
<td>H/H</td>
<td>15/45</td>
<td>Potassium</td>
<td>4.3</td>
<td>Albumin</td>
<td>2.0</td>
</tr>
<tr>
<td>Platelets</td>
<td>276</td>
<td>Chloride</td>
<td>110</td>
<td>AST</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bicab</td>
<td>23</td>
<td>ALT</td>
<td>33</td>
</tr>
<tr>
<td>Creatinine</td>
<td>41</td>
<td></td>
<td></td>
<td>TBili</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucose</td>
<td>2.0</td>
<td>DBili</td>
<td>2.0</td>
</tr>
</tbody>
</table>

UA: 3+ protein, 2-5WBcs, 5-10RBCs
UPr/Cr: 1189g/91g = 13g
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</thead>
<tbody>
<tr>
<td><strong>HbA1C</strong></td>
<td>6.1</td>
<td>HIV</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td><strong>HBsAg</strong></td>
<td>Negative</td>
<td>ANA</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td><strong>HBsAb</strong></td>
<td>Negative</td>
<td>C3</td>
<td>94 (75-140)</td>
<td></td>
</tr>
<tr>
<td><strong>HCV Ab</strong></td>
<td>Negative</td>
<td>C4</td>
<td>32 (10-34)</td>
<td></td>
</tr>
</tbody>
</table>

**Lipid Panel**

- Total Cholesterol: 209
- LDL: 139
- HDL: 51
- TG: 97
• EKG: Normal Sinus Rhythm

• Chest X-Ray: B/L pleural effusions and atelectasis.

• ECHO: EF: 65%. Moderate concentric LV hypertrophy. Mitral inflow pattern c/w impaired relaxation and small pericardial effusion – may be consistent with an infiltrative process

• Abdominal US: Moderate ascites. R kidney: 11.8cm  L kidney: 11.5cm Increased bilateral cortical echogenicity. No hydronephrosis or calculi.
Work-Up

- **SPEP**: hypoalbuminemia with peak in beta-gamma region
- **UPEP**: albumin and other serum proteins with 2 peaks in gamma region. Pattern compatible with monoclonal gammopathy.
- **UIFE**: weak Bence Jones protein Lambda type
- **SIFE**: Two IgA lambda bands identified
  - IgA: 627  IgG: 450  IgM: 68
- **Serum Free Ig Light chains**
  - Kappa: 26.2
  - Lambda: 595
  - K/L: .04
- **B2 microglobulin**: 4.3 (0.8-2.2)
Work-up

- Cardiac MRI: Increase in LV and RV wall thickness. On delayed contrast enhanced images there is diffuse rapid nulling of the entire myocardium as is typically seen in amyloidosis.

- Fat Pad biopsy: negative for amyloid
Differential Diagnosis

- Primary Amyloidosis
- Light chain deposition disease
- Myeloma Cast Nephropathy
Renal Biopsy
Primary Amyloidosis
Amyloidosis

- A family of disorders defined by the extracellular deposition of protein fibrils with a characteristic B-pleated sheet conformation
- To date, about 30 different amyloidogenic proteins have been identified
- Described as “chameleon” proteins due to their ability to acquire more than one conformation - classified based on precursor proteins
Pathology

- Abnormal folding of an extracellular protein that is normally soluble
- In AL amyloid it is the result of either a proteolytic event or an AA sequence that makes a light chain thermodynamically unstable and prone to self aggregation
- Aggregates form protofilaments that associate into amyloid fibrils
- Serum amyloid P protein (SAP) interacts with the amyloid fibrils promoting fibril formation and aggregation
Contiguous B-sheet polypeptide chains wind around one another to form an amyloid fibril with a distinct diameter of 7.5-10nm visible on EM.

Ultrastructure of the fibril allows the intercalation of Congo red dye.
# Types of Systemic Amyloidosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Precursor Protein</th>
<th>Amyloid Protein</th>
<th>Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL amyloidosis</td>
<td>Monoclonal Ig light chain</td>
<td>AL</td>
<td>Kidney, heart, liver, gastrointestinal tract, spleen, nervous system, soft tissue, thyroid, adrenal gland</td>
</tr>
<tr>
<td>AH amyloidosis</td>
<td>Monoclonal Ig heavy chain</td>
<td>AH</td>
<td>Extremely rare; kidney involvement predominates in the small number of reported cases</td>
</tr>
<tr>
<td>AA amyloidosis</td>
<td>Serum amyloid A (SAA)</td>
<td>AA</td>
<td>Kidney, liver, gastrointestinal tract, spleen, autonomic nervous system, thyroid</td>
</tr>
<tr>
<td>Transthyretin amyloidosis (hereditary)</td>
<td>Transthyretin</td>
<td>ATTR</td>
<td>Peripheral nervous system, heart, vitreous opacities; kidney involvement is not typical</td>
</tr>
<tr>
<td>Fibrinogen Aα amyloidosis (hereditary)</td>
<td>Fibrinogen Aα chain</td>
<td>AFib</td>
<td>Kidney, liver, spleen; hypertension is common; kidney involvement is predominantly glomerular</td>
</tr>
<tr>
<td>Apolipoprotein AI amyloidosis (hereditary)</td>
<td>Apolipoprotein AI</td>
<td>AApAI</td>
<td>Kidney (with predominant medullary deposition), liver, heart, skin, larynx</td>
</tr>
<tr>
<td>Apolipoprotein AII amyloidosis (hereditary)</td>
<td>Apolipoprotein AII</td>
<td>AApAI</td>
<td>Kidney</td>
</tr>
<tr>
<td>Lysozyme amyloidosis (hereditary)</td>
<td>Lysozyme</td>
<td>ALys</td>
<td>Kidney, liver, gastrointestinal tract, spleen, lymph nodes, lung, thyroid, salivary glands</td>
</tr>
<tr>
<td>Gelsolin amyloidosis (hereditary)</td>
<td>Gelsolin</td>
<td>AGel</td>
<td>Cranial nerves, lattice corneal dystrophy</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy (hereditary)</td>
<td>Cystatin C</td>
<td>ACys</td>
<td>Cerebral vessels</td>
</tr>
<tr>
<td>Senile systemic amyloidosis</td>
<td>Transthyretin (wild type)</td>
<td>ATTR</td>
<td>Heart, soft tissue</td>
</tr>
<tr>
<td>Dialysis-related amyloidosis</td>
<td>β2-Microglobulin</td>
<td>Aβ2M</td>
<td>Osteoarticular tissue; less common sites are gastrointestinal tract, blood vessels, heart</td>
</tr>
</tbody>
</table>
Diagnosis

- Abdominal fat biopsy
  - Sensitivity of Congo red staining of abdominal fat is approximately 80-90% and 65-75% in AL and AA amyloidosis

- Renal Biopsy
  - Likelihood of a missed diagnosis is lower with a kidney biopsy than with biopsies of other tissues because amyloid fibrils are visible with EM
Light-chain (AL) Amyloidosis

- Most-common type of systemic amyloidosis and most severe form affecting the kidney
- Amyloid protein is an Ig light chain that is produced by a clonal population of plasma cells in the bone marrow
- Clonal plasma cells express light chains of the lambda isotype more frequently than the kappa, with a ratio of 3:1
- Incidence is 9 million per year with 10-15% occurring in association with MM
- Prognosis of untreated AL amyloid is survival time of 12 months and with treatment now exceeds 3 years.
Clinical Presentations

- Nephrotic Syndrome
- Restrictive cardiomyopathy
- Hepatomegaly
- Soft tissue involvement
Treatment

- High Dose Melphalan + ASCT
- Dexamethasone + Melphalan
- CyBorD
Randomized comparison of high dose melphalan + autologous hematopoietic stem cell transplant with standard dose melphalan + high dose dexamethasone

Multicenter, randomized, controlled trial including 100 patients

Primary outcome: overall survival
Results

- High-dose melphalan + ASCT was not superior to the outcome with standard dose melphalan + dexamethasone

- Treatment related mortality in the HDM group (24%) was higher (13%)

Jaccard A et al; NEJM 2007
Largest study of CyBor D for the initial treatment of AL amyloidosis

Series of 230 patients from 2 European referral centers

Overall hematologic response rate was 60%; cardiac at 17% and renal response rate at 25%

After a medium follow-up of 25 months, estimate overall survival at 3 years was 55%
Proteinuria after SCT

![Graph showing change in proteinuria over time after SCT. The x-axis represents follow-up months since stem cell transplantation, ranging from 0 to 72 months. The y-axis represents the change in proteinuria, ranging from -100% to 60%. Two lines are depicted: one for responders and one for non-responders. The graph shows a decrease in proteinuria over time, with responders showing a sharper decrease compared to non-responders.]
Survival based on renal response

Am J kidney Disease 20010; 6: 270-277
Transplant in AL Amyloidosis

- Patient survival and graft survival analyzed in 21 renal transplantation patients – 3 living and 18 deceased donor grafts
- Medium estimated patient survival was 89 months
- One and Five year survival rates were 95.2% and 71.4%
- There were no graft failures as a result of recurrent amyloid
- At five years there was scintigraphy evidence of recurrent amyloid in 6 functioning renal allografts accompanied in 5 patients with proteinuria

Pinney et Al; J of Clinical Oncology 2011